Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

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Introduction (Last updated June 17, 2013; last reviewed May 7, 2013)

Prior to the widespread use of potent combination antiretroviral therapy (ART), opportunistic infections (OIs), which have been defined as infections that are more frequent or more severe because of immunosuppression in HIV-infected persons,[1,2] were the principal cause of morbidity and mortality in this population. In the early 1990s, the use of chemoprophylaxis, immunization, and better strategies for managing acute OIs contributed to improved quality of life and improved survival.[3] Subsequently, the widespread use of potent ART has had the most profound influence on reducing OI-related mortality in HIV-infected persons.[3-10]

Despite the availability of ART, OIs continue to cause considerable morbidity and mortality in the United States for three main reasons:

1. Approximately 20% of HIV-infected persons in the United States are unaware of their HIV infection,[11,12] and many present with an OI as the initial indicator of their disease;[13]
2. Some individuals are aware of their HIV infection, but do not take ART due to psychosocial or economic factors; and
3. Some patients are enrolled in HIV care and prescribed ART, but do not attain an adequate virologic and immunologic response due to inconsistent retention in care, poor adherence, unfavorable pharmacokinetics, or unexplained biologic factors.[6,14,15]

Recent analyses suggest that while 77% of HIV-infected persons who are retained in care and prescribed ART are virologically suppressed, only 20% to 28% of the total estimated HIV-infected population in the United States are virologically suppressed,[11,16] with as few as 10% in some jurisdictions.[17] Thus, while hospitalizations and deaths have decreased dramatically due to ART, OIs continue to cause substantial morbidity and mortality in HIV-infected persons.[18-28] Clinicians must be knowledgeable about optimal strategies for diagnosis, prevention, and treatment of OIs to provide comprehensive, high quality care for these patients.

It is important to recognize that the relationship between OIs and HIV infection is bi-directional. HIV causes the immunosuppression that allows opportunistic pathogens to cause disease in HIV-infected persons. OIs, as well as other co-infections that may be common in HIV-infected persons, such as sexually transmitted infections (STIs), can adversely affect the natural history of HIV infection by causing reversible increases in circulating viral load[29-34] that could accelerate HIV progression and increase transmission of HIV.[35] Thus, while chemoprophylaxis and vaccination directly prevent pathogen-specific morbidity and mortality, they may also contribute to reduced rate of progression of HIV disease. For instance, randomized trials have shown that chemoprophylaxis with trimethoprim-sulfamethoxazole can both decrease OI-related morbidity and improve survival. The survival benefit is likely to result, in part, from reduced progression of HIV infection.[36-40] In turn, the reduced progression of HIV infection would reduce the risk of subsequent OIs.

History of These Guidelines

In 1989, the Guidelines for Prophylaxis against *Pneumocystis carinii* Pneumonia for Persons Infected with the Human Immunodeficiency Virus became the first HIV-related treatment guideline published by the U.S. Public Health Service.[41] This publication was followed by a guideline on prevention of *Mycobacterium avium* complex disease in 1993.[42] In 1995 these guidelines were expanded to include the prevention of all HIV-related OIs and the Infectious Diseases Society of America (IDSA) joined as a co-sponsor.[43] These prevention guidelines were revised in 1997, 1999, and 2002 and were published in *Morbidity and Mortality Weekly Report (MMWR)*,[44-46] *Clinical Infectious Diseases*,[47-49] *The Annals of Internal Medicine*,[50,51] *American Family Physician*,[52,53] and *Pediatrics*;[54] accompanying editorials appeared in the *Journal of the American Medical Association (JAMA)*[2,55] and in *Topics in HIV Medicine*.[56]

In 2004 the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and the HIV Medicine Association (HIVMA) of the IDSA published a new guideline including recommendations for treating OIs among HIV-infected adults and adolescents.[57] Companion guidelines were published for HIV-infected children.[58] Revised guidelines for both prevention and treatment of OIs in HIV-infected adults and adolescents[59] and HIV-exposed/infected children[60] were published in 2009.

Responses to these guidelines (e.g., numbers of requests for reprints, website contacts) demonstrate that these documents are valuable references for HIV health care providers. The inclusion of ratings that indicate both the strength of each recommendation and the quality of supporting evidence allows readers to assess the relative importance of each recommendation. The present revision includes recommendations for prevention and treatment of OIs in HIV-infected adults and adolescents; a revision of recommendations for HIV-exposed and infected children can also be found in http://www.aidsinfo.nih.gov.

These guidelines are intended for clinicians, other health care providers, HIV-infected patients, and policy makers in the United States; guidelines pertinent to other regions of the world, especially resource-limited countries, may differ with respect to the spectrum of OIs of interest and diagnostic and therapeutic capacities.

Guidelines Development Process

These guidelines were prepared by the Opportunistic Infections Working Group under the auspices of the Office of AIDS Research Advisory Council (OARAC) of the NIH. Briefly, six co-editors selected and appointed by their respective agencies (i.e., NIH, CDC, IDSA) convened working groups of clinicians and scientists with subject matter expertise in specific OIs. The co-editors appointed a leader for each working group, which reviewed the literature since the last publication of these guidelines, conferred over a period of several months, and produced draft revised recommendations. Issues requiring specific attention were reviewed and discussed by the co-editors and the leaders from each working group at the annual meeting of the IDSA in Vancouver, Canada, in October 2010. After further revision, the guidelines were reviewed by patient care advocates and by primary care providers with extensive experience in the management of HIV infection. The final document reflects further revision by the co-editors, the Office of AIDS Research (OAR), experts at CDC, and by the IDSA and affiliated HIV Medicine Association prior to final approval and publication on the AIDS*info* website. The names and affiliations of all contributors as well as their financial disclosures are provided in the Panel roster and Financial Disclosure section (Appendix C). The names of the patient advocates and primary HIV care providers who reviewed the document are listed in Contributors (Appendix D).

Guidelines Development Process (page 1 of 2)

Topic	Comment
Goal of the guidelines	Provide guidance to HIV care practitioners on the optimal prevention and management of HIV-related opportunistic infections (OIs) for adults and adolescents in the United States.
Panel members	The panel is composed of six co-editors who represent the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the HIV Medicine Association of the Infectious Disease Society of America (HIVMA/IDSA), plus more than 100 members who have expertise in HIV clinical care, infectious disease management, and research. Co-editors are appointed by their respective agencies or organizations. Panel members are selected from government, academia, and the healthcare community by the co-editors and assigned to a working group for one or more the guideline's sections based on the member's area of subject mater expertise. Each working group is chaired by a single panel member selected by the co-chairs. Members serve on the panel for a 4-year term, with an option to be reappointed for additional terms. The panel co-editors also select members from the community of persons affected by HIV disease (i.e., adults living with HIV infection, advocates for persons living with HIV infection) to review the entire guidelines document. The lists of the current panel members and of the patient advocates and primary HIV care providers who reviewed the document can be found in Appendices C and D, respectively.
Financial disclosure and management of conflicts of interest	All members of the panel submit a written financial disclosure annually reporting any associations with manufacturers of drugs, vaccines, medical devices, or diagnostics used to manage HIV-related OIs. A list of these disclosures and their last update is available in Appendix C. The panel co-editors review each reported association for potential conflict of interest and determine the appropriate action: disqualification from the panel, disqualification/recusal from topic review and discussion; no disqualification needed. A conflict of interest is defined as any direct financial interest related to a product addressed in the section of the guideline to which a panel member contributes content. Financial interests include direct receipt by the panel member of payments, gratuities, consultancies, honoraria, employment, grants, support for travel or accommodation, or gifts from an entity having a commercial interest in that product. Financial interest also includes direct compensation for membership on an advisory board, data safety monitoring board, or speakers' bureau. Compensation and support that filters through a panel member's university or institution (e.g., grants, research funding) is not considered a conflict of interest.
Users of the guidelines	HIV treatment providers
Developer	Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents—a working group of the Office of AIDS Research Advisory Council (OARAC).
Funding source	The Office of AIDS Research (OAR), NIH
Evidence collection	The recommendations in the guidelines are generally based on studies published in peer-reviewed journals. On some occasions, particularly when new information may affect patient safety, unpublished data presented at major conferences or information prepared by the U.S. Food and Drug Administration or manufacturers (e.g., warnings to the public) may be used as evidence to revise the guidelines. Panel members of each working group are responsible for conducting a systematic comprehensive review of the literature, for conducting updates of that review, and for bringing to their working group's attention all relevant literature.
Method of synthesizing data and formulating recommendations	Each section of the guidelines is assigned to a working group of panel members with expertise in the area of interest. The members of the working group synthesize the available data. Recommendations are reviewed and updated by each working group after an assessment of the quality and impact of the existing and any new data. Aspects of evidence that are considered include but are not necessarily limited to the type of study (e.g., case series, prospective cohort, randomized controlled trial), the quality and appropriateness of the methods, and the number of subjects and effect sizes observed. Each revision of the guidelines is reviewed by patient care advocates and by primary care providers with extensive experience in the management of HIV infection to assess cultural sensitivity and operational utility. Finally, all material is reviewed by the co-editors, OAR, subject matter experts at CDC and the HIVMA/IDSA prior to final approval and publication.
Recommendation rating	Recommendations are rated using a revised version of the previous rating system (see How to Use the Information in this Report and Rating System for Prevention and Treatment Recommendations, below) and accompanied, as needed, by explanatory text that reviews the evidence and the working group's assessment. All proposals are discussed at teleconferences and by email and then assessed by the panel's co-editors and reviewed by OAR, CDC, and the HIVMA/IDSA before being endorsed as official recommendations.

Guidelines Development Process (page 2 of 2)

Topic	Comment
Other guidelines	These guidelines focus on prevention and treatment of HIV-related OIs for adults and adolescents. A separate guideline outlines similar recommendations for HIV-infected and exposed children. These guidelines are also available on the AIDS*info* website (http://www.aidsinfo.nih.gov).
Update plan	Each work group and the co-editors meet at least every 6 months by teleconference to review data that may warrant modification of the guidelines. Updates may be prompted by approvals of new drugs, vaccines, medical devices or diagnostics, by new information regarding indications or dosing, by new safety or efficacy data, or by other information that may affect prevention and treatment of HIV-related OIs. Updates that may significantly affect patient safety or treatment and that warrant rapid notification may be posted temporarily on the AIDS*info* website (http://www.aidsinfo.nih.gov) until appropriate changes can be made in the guidelines document.
Public comments	After release of an update on the AIDS*info* website, the public is given a 2-week period to submit comments to the panel. These comments are reviewed, and a determination is made by the appropriate work group and the co-editors as to whether revisions are indicated. The public may also submit comments to the Panel at any time at contactus@aidsinfo.nih.gov.

Major Changes in Guidelines Since Last Publication

Major changes in the document include:

1) New information on when to start ART in the setting of an acute OI, including tuberculosis;
2) When to start therapy for hepatitis B and hepatitis C disease, and what drugs to use;
3) Drug interactions between drugs used to manage OIs and HIV;
4) A change in the system for rating the strength of each recommendation, and the quality of evidence supporting that recommendation (see Rating System for Prevention and Treatment Recommendations); and
5) Inclusion of pathogen-specific tables of recommended prevention and treatment options at the end of each OI section, in addition to summary tables at the end of the document.

How to Use the Information in this Report

Recommendations in this report address:

1) Preventing exposure to opportunistic pathogens;
2) Preventing disease;
3) Discontinuing primary prophylaxis after immune reconstitution;
4) Treating disease;
5) When to start ART in the setting of an acute OI;
6) Monitoring for adverse effects (including immune reconstitution inflammatory syndrome [IRIS]);
7) Managing treatment failure;
8) Preventing disease recurrence ("secondary prophylaxis" or chronic maintenance therapy);
9) Discontinuing secondary prophylaxis after immune reconstitution; and
10) Special considerations during pregnancy.

Recommendations are rated using a revised version of the previous rating system (see Rating System for Prevention and Treatment Recommendations below) and accompanied, as needed, by explanatory text that

reviews the evidence and the working group's assessment. In this system, the letters A, B, or C signify the strength of the recommendation for or against a preventive or therapeutic measure, and Roman numerals I, II, or III indicate the quality of evidence supporting the recommendation. In cases where there were no data for the prevention or treatment of an OI based on studies conducted in HIV-infected populations, but data derived from HIV-uninfected persons existed that could plausibly guide management of HIV-infected patients, the recommendation is rated as a II or III but is assigned A, B, or C depending on the strength of the recommendation.

Rating System for Prevention and Treatment Recommendations

Strength of Recommendation	Quality of Evidence for the Recommendation
A: Strong recommendation for the statement	**I:** One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
B: Moderate recommendation for the statement	**II:** One or more well-designed, non-randomized trials or observational cohort studies with long-term clinical outcomes
C: Optional recommendation for the statement	**III:** Expert opinion

This document also includes tables in each OI section pertinent to the prevention and treatment of OIs, as well as eight summary tables at the end of the document (Tables 1–8), a figure that includes immunization recommendations, and an appendix that summarizes recommendations pertinent to preventing exposure to opportunistic pathogens, including preventing exposure to STIs (Appendix A).

Special Considerations Regarding Pregnancy

No large studies have been conducted concerning the epidemiology or manifestations of HIV-associated OIs among pregnant women. No data demonstrate that the spectrum of OIs differs from that among non-pregnant women with comparable CD4+ counts.

Physiologic changes during pregnancy can complicate the recognition of OIs and complicate treatment due to changes in pharmacokinetic parameters, which may influence optimal dosing for drugs used for prevention or treatment of OI. Factors to consider include the following:[61]

- Increased cardiac output by 30% to 50% with concomitant increase in glomerular filtration rate and renal clearance.
- Increased plasma volume by 45% to 50% while red cell mass increases only by 20% to 30%, leading to dilutional anemia.
- Tidal volume and pulmonary blood flow increase, possibly leading to increased absorption of aerosolized medications. The tidal volume increase of 30% to 40% should be considered if ventilator assistance is required.
- Placental transfer of drugs, increased renal clearance, altered gastrointestinal absorption, and metabolism by the fetus that might affect maternal drug levels.
- Limited pharmacokinetic data are available; use usual adult doses based on current weight, monitor levels if available, and consider the need to increase doses if the patient is not responding as expected.

Non-invasive imaging, including imaging that may expose a patient to radiation, is an important component of OI diagnosis. Fetal risk is not increased with cumulative radiation doses below 5 rads; the majority of imaging studies result in radiation exposure to the fetus that is lower than the 5-rad recommended limit. In humans, the primary risks associated with high-dose radiation exposure are growth restriction, microcephaly,

and developmental disabilities. The most vulnerable period is 8 to 15 menstrual weeks of gestation, with minimal risk before 8 weeks and after 25 weeks. The apparent threshold for development of mental retardation is 20 to 40 rads, with risk of more serious mental retardation increasing linearly with increasing exposure above this level. Among children, risk for carcinogenesis might be increased approximately 1 per 1000 or less per rad of in utero radiation exposure.[62] Therefore, pregnancy should not preclude usual diagnostic evaluation when an OI is suspected.[63] Abdominal shielding should be used when feasible to further limit radiation exposure to the fetus. Experience with use of magnetic resonance imaging (MRI) in pregnancy is limited, but no adverse fetal effects have been noted.[64]

Other procedures necessary for diagnosis of suspected OIs should be performed in pregnancy as indicated for non-pregnant patients. A pregnant woman who is >20 weeks of gestation should not lie flat on her back but should have her right hip elevated with a wedge to displace the uterus off the great vessels and prevent supine hypotension. Oxygenation should be monitored when pregnant patients are positioned such that ventilation or perfusion might be compromised.

In the United States, pregnancy is an indication to start antiretroviral therapy if the HIV-infected woman is not already on therapy. A decision to defer therapy based on a current or recent OI should be made on the same basis as for non-pregnant individuals supplemented by consultation with the obstetrician regarding factors unique to each individual pregnancy.

After first-trimester exposure to agents of uncertain teratogenic potential, including many of the anti-infective agents described in this guideline, an ultrasound should be conducted every 4 to 6 weeks in the third trimester to assess fetal growth and fluid volume, with antepartum testing if growth lag or decreased fluid are noted.

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